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CLINICAL RESEARCH

Coronary Artery Disease

Differential Associations Between Specific Depressive Symptoms and Cardiovascular Prognosis in Patients With Stable Coronary Heart Disease

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Objectives

The purpose of this research was to evaluate the relationship between cognitive and somatic depressive symptoms and cardiovascular prognosis.

Background

Depression in patients with stable coronary heart disease (CHD) is associated with poor cardiac prognosis. Whether certain depressive symptoms are more cardiotoxic than others is unknown.

Methods

In the Heart and Soul Study, 1,019 patients with stable CHD were assessed using the Patient Health Questionnaire to determine the presence of the 9 depressive symptoms included in the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition. The mean age of the patients was 67 years, and 82% were men. A comparison was made on a new cardiovascular event (myocardial infarction, stroke, transient ischemic attack, or congestive heart failure) or death (mean follow-up duration 6.1 ± 2.0 years) on the basis of cognitive and somatic sum scores and for patients with or without each of those specific depressive symptoms. Demographic characteristics, cardiac risk factors, and cardiac medications were controlled for.

Results

After adjustment for demographic data and cardiac risk factors, each somatic symptom was associated with 14% greater risk for events (hazard ratio [HR]: 1.14; 95% confidence interval [CI]: 1.05 to 1.24; $p = 0.002$). Fatigue (HR: 1.34; 95% CI: 1.07 to 1.67; $p = 0.01$), appetite problems (HR: 1.46; 95% CI: 1.12 to 1.91; $p = 0.005$), and sleeping difficulties (HR: 1.26; 95% CI: 1.00 to 1.58; $p = 0.05$) were most strongly predictive of cardiovascular events. In contrast, cognitive symptoms (HR: 1.08; 95% CI: 0.99 to 1.17; $p = 0.09$) were not significantly associated with cardiovascular events.

Conclusions

In patients with stable CHD, somatic symptoms of depression were more strongly predictive of cardiovascular events than cognitive symptoms, although the CIs surrounding these estimates had substantial overlap. These findings are highly consistent with those of previous studies. Further research is needed to understand the pathophysiological processes by which somatic depressive symptoms contribute to prognosis in patients with CHD. (J Am Coll Cardiol 2010;56:838–44) © 2010 by the American College of Cardiology Foundation

By 2020, the most important causes of disability-adjusted life-years are predicted to be coronary heart disease (CHD) and major depression (1). Patients with CHD are at increased risk for developing depression (2). Likewise, patients with depression are at increased risk for developing

cardiovascular (CV) disease, including congestive heart failure, myocardial infarction (MI), stroke, and CV death (3–5). In recent decades, the effects of depression in patients with CHD have been extensively studied (3,6,7). Several randomized controlled trials have been undertaken to eval-

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Federation for Aging Research; the Generalist Physician Faculty Scholars Program of the Robert Wood Johnson Foundation; the Ischemia Research and Education Foundation; and the Nancy Kirwan Heart Research Fund. The funding organizations had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript. Dr. de Jonge was supported by VIDI grant 016.086.397 from the Dutch Medical Research Council. All other authors have reported that they have no relationships to disclose.

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uate the efficacy of antidepressant therapy in patients with CHD. However, in most of these studies, treatment had only minor effects on reducing depressive symptoms (8).

A reason for these findings may be the heterogeneity of depression as a syndrome (9). Depression is a syndrome consisting of 9 depressive symptoms, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (10). Several researchers over time have distinguished somatic symptoms from cognitive symptoms of depression (11–13). In recent years, this distinction has been applied to patients with CHD (14). It has been found that somatic symptoms of depression had a relatively high prevalence (15) and were more strongly associated with CV prognosis (14,16–18), medical comorbidity (13), and heart rate variability (19). At this time, it remains to be determined which of these symptoms has the most cardiotoxic contribution in terms of CV prognosis in patients with stable CHD.

We hypothesized the existence of differential associations of specific depressive symptoms with CV prognosis. We chose to investigate this research question in a population with stable CHD because in this sample, depressive symptoms may be less confounded by symptoms that are frequently expressed in the direct aftermath of an acute coronary event, such as fatigue. The identification of certain cardiotoxic symptoms within the diagnosis of depression would be an important step in the development of antidepressive interventions that aim to alleviate the depression-associated risk of CV events.

Methods

Design and patients. This study was based on data from the Heart and Soul Study, a prospective cohort study focused on psychosocial factors and health outcomes in patients with stable CHD. Details regarding the methods of the Heart and Soul Study have been described previously (20). Patients had to meet the following inclusion criteria: 1) history of MI or coronary revascularization; 2) angiographic evidence of at least 50% stenosis in at least 1 coronary vessel; and 3) a diagnosis of CHD by an internist or cardiologist. Exclusion criteria were 1) a history of MI in the past 6 months; 2) poor exercise tolerance (inability to walk 1 block); and 3) planning to move from the local area within 3 years.

We initially mailed letters to 15,438 patients who had International Classification of Diseases-9th Revision codes for CHD based on administrative databases at 2 U.S. Department of Veterans Affairs medical centers, 1 university medical center, and 9 public health clinics in northern California. Because administrative data are not necessarily correct or current, many of these letters were mailed to bad addresses or to persons who did not meet eligibility criteria. Of the 2,495 patients who returned the form indicating that they would be interested in participating, 370 were excluded on the basis of the pre-defined exclusion criteria, and 505 could not be reached by

telephone. Of the 1,620 patients who were confirmed to meet the eligibility criteria, 596 declined to participate, and 1,024 (63%) enrolled. Between September 2000 and December 2002, all participants completed a baseline assessment, including a medical history interview, a fasting blood draw, a physical examination, an exercise treadmill test with stress echocardiography, a comprehensive health status questionnaire, and 24-h urine collection. All participating patients signed informed consent forms. The study protocol was approved by the institutional review boards of the participating hospitals.

Baseline characteristics. Baseline characteristics of the study sample included sociodemographic data, history of CV disease, and cardiac disease severity. The sociodemographic characteristics were age, sex, and marital status and were determined by questionnaire. History of CV disease was determined by self-report and included MI, congestive heart failure, and stroke. All participants underwent resting echocardiography using an Acuson Sequoia ultrasound system (Siemens Medical Solutions USA, Inc., Mountain View, California) with a 3.5-MHz transducer. Standard 2-dimensional views and performed planimetry with a computerized digitization system were obtained to determine left ventricular ejection fraction. Smoking was determined by self-report, and body mass index was assessed. Participants were instructed to bring their medication bottles to their appointments, and study personnel recorded all current medications, including dose and frequency use.

Assessment of depressive symptoms. The 9-item Patient Health Questionnaire (PHQ) (10) was used to determine the presence and severity of the 9 depressive symptoms listed in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition. The PHQ is a self-report checklist derived from the interview used in the Primary Care Evaluation of Mental Disorders (21). This instrument measures the presence of depressive symptoms during the previous 2 weeks, each scored as follows: 0 = not at all, 1 = several days, 2 = more than one-half of the days, or 3 = nearly every day.

This study evaluated the effect of each depressive symptom both as a dichotomous variable using the standard cut point of ≥ 2 for the presence of the first 8 depressive symptoms and ≥ 1 for the presence of the symptom suicidal ideation (in concordance with the manual) (10) and as a log-transformed continuous variable. The 9 symptoms of depression in the PHQ, based on the classification of depression in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, are: 1) depressed mood; 2) loss of interest; 3) appetite problems; 4) sleeping difficulties; 5) psychomotor agitation or retardation; 6) fatigue; 7) feelings of worthlessness; 8) concentration problems; and 9) suicidal ideation.

Abbreviations and Acronyms
CHD = coronary heart disease
CI = confidence interval
CV = cardiovascular
HR = hazard ratio
MI = myocardial infarction
PHQ = Patient Health Questionnaire

Somatic and cognitive depressive symptoms. Following earlier work, depressive symptoms were categorized as follows: depressed mood, lack of interest, worthlessness, concentration problems, and suicidal ideation were considered to be cognitive symptoms, and appetite problems, sleeping difficulties, psychomotor agitation or retardation, and fatigue were considered to be somatic symptoms (18,19).

End points and follow-up. After the baseline examination, we conducted annual telephone follow-up interviews with participants (or their proxies), asking specifically about hospitalization for “heart trouble.” For any reported event, medical records, electrocardiograms, death certificates, and coroners’ reports were retrieved and reviewed by 2 independent blinded adjudicators. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator as necessary. The primary study end points were CV events, including heart failure, MI, stroke, transient ischemic attack, or death.

For patients to be diagnosed with heart failure, they had to be hospitalized for a clinical syndrome meeting at least 2 of the following criteria: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, and cardiomegaly or pulmonary edema on chest radiography. A clear change in these symptoms from the patients’ usual clinical status and either peripheral hypoperfusion (in the absence of other causes) or peripheral or pulmonary edema requiring intravenous diuretic, inotropic, or vasodilator therapy was a necessary condition (22). Standard criteria were used for defining nonfatal MI (23). Stroke was defined as new neurological deficit, which must not have been the result of brain trauma, tumor, infection, or other cause. Transient ischemic attack was defined as a focal neurological deficit (in the absence of head trauma) lasting between 30 s and 24 h, with rapid evolution of the symptoms to the maximal level of deficit in <5 min and with subsequent complete resolution. Death was determined by death certificates and coroners’ reports.

Statistical analysis. We used Cox proportional hazards regression (i.e., survival analysis) to estimate the differential effects of the 9 depressive symptoms on cardiac events. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. The Cox regression procedure is a method of estimating time-to-event models in the presence of censored cases. Cases are censored either at the occurrence of the first CV event or at the end of follow-up, whichever comes first. Cox regression analyses were conducted for evaluating the effects of each specific depressive symptom, controlling for age and sex. Second, multivariate effects were evaluated after controlling for variables previously found to predict CV events in this cohort (age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, and smoking) (22) and for use of cardioprotective medications (aspirin, beta-blockers, statins, and renin-angiotensin system inhibitors). Each depressive symptom was entered both as a log-transformed continuous variable and as a dichotomous

variable. Interactions were checked between the specific depressive symptoms and sex and age. All statistical analyses were performed using SPSS version 14.0 (SPSS, Inc., Chicago, Illinois).

Results

Of the 1,024 enrolled patients with CHD, 1,019 (>99%) were available for follow-up. Patient characteristics are presented in Table 1. The prevalence of each specific depressive symptom is presented in Table 2. A total of 399 events occurred (MI, heart failure, stroke, transient ischemic attack, or death) during an average of 6.1 ± 2.0 years of follow-up.

In age-adjusted analyses, both somatic and cognitive symptoms were associated with an increased risk for CV events. The annual rate of events ranged from 5.9% among those with no somatic symptoms to 12.6% among those with 4 somatic symptoms and from 6.4% among those with no cognitive symptoms to 11.4% among those with 5 cognitive symptoms (Fig. 1). Each somatic symptom was associated with a 21% increased rate of CV events (HR: 1.21; 95% CI: 1.11 to 1.31; $p < 0.0001$), and this association remained strong after adjustment for potential confounding variables (HR: 1.14; 95% CI: 1.05 to 1.24) (Table 2). Each cognitive symptom was associated with a 12% increased rate of CV events in age-adjusted analyses (HR: 1.12; 95% CI: 1.03 to 1.21; $p = 0.006$). After further adjustment for potential confounding variables, the cognitive sum score did not significantly predict CV events (HR: 1.08; 95% CI: 0.99 to 1.17; $p = 0.09$).

When entered as dichotomous variables, several symptoms were associated with CV events in age-adjusted models. After further adjustment for age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, and use of cardioprotective medications, 3 of the

Table 1 Baseline Characteristics of the Study Sample (n = 1,019)

Age (yrs)	67 ± 11
Men	836 (82%)
Married	436 (43%)
History of MI	545 (54%)
History of CHF	179 (18%)
History of stroke	148 (15%)
Diabetes mellitus	265 (26%)
Left ventricular ejection fraction	0.62 ± 0.10
Current smoking	199 (20%)
Body mass index (kg/m ²)	28 ± 5
Aspirin	790 (78%)
Beta-blockers	591 (58%)
Statins	655 (64%)
Renin-angiotensin system inhibitors	524 (51%)
Antidepressant agents	187 (18%)

Data are expressed as mean ± SD or as n (%).
CHF = congestive heart failure; MI = myocardial infarction.

Table 2 Age-Adjusted Annual Rate of CV Events (MI, CHF, Stroke, TIA, or Death) Among Participants With and Without Specific Depressive Symptoms

Symptom	With Symptoms		Without Symptoms		Age-Adjusted HR (95% CI)	p Value	Fully Adjusted HR (95% CI)*	p Value
	n	Age-Adjusted Event Rate	n	Age-Adjusted Event Rate				
Somatic symptoms								
Fatigue	267	9.1%	746	6.1%	1.49 (1.20–1.84)	0.0003	1.34 (1.07–1.67)	0.01
Appetite problems	160	11.1%	858	6.2%	1.76 (1.37–2.28)	<0.0001	1.46 (1.12–1.91)	0.005
Psychomotor agitation/retardation	85	9.3%	934	6.7%	1.39 (0.99–1.95)	0.06	1.31 (0.93–1.85)	0.13
Sleeping difficulties	249	8.7%	766	6.3%	1.38 (1.11–1.72)	0.004	1.26 (1.00–1.58)	0.05
Somatic sum score†					1.21 (1.11–1.31)	<0.0001	1.14 (1.05–1.24)	0.002
Cognitive symptoms								
Depressed mood	114	9.7%	900	6.6%	1.48 (1.10–1.99)	0.01	1.32 (0.97–1.80)	0.08
Lack of interest	129	9.8%	889	6.5%	1.50 (1.14–1.97)	0.004	1.21 (0.91–1.61)	0.19
Worthlessness	114	9.1%	904	6.6%	1.36 (0.99–1.86)	0.06	1.22 (0.88–1.69)	0.23
Concentration problems	129	8.2%	890	6.7%	1.22 (0.90–1.64)	0.19	1.10 (0.81–1.49)	0.55
Suicidal ideation	111	8.4%	908	6.7%	1.26 (0.92–1.71)	0.15	1.25 (0.91–1.72)	0.18
Cognitive sum score†					1.12 (1.03–1.21)	0.006	1.08 (0.99–1.17)	0.09

*Adjusted for age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking aspirin, beta-blocker use, statin use, and renin-angiotensin system inhibitor use. †Entered as a continuous variable.

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; TIA = transient ischemic attack; other abbreviations as in Table 1.

somatic symptoms (fatigue, appetite problems, and sleeping difficulties) were independently predictive of CV events (Table 2). These were also the 3 most common symptoms. None of the cognitive symptoms were independently predictive of CV events. We observed no evidence for an interaction of specific depressive symptoms with age or sex in predicting CV events (all p values for interaction = NS). In Figure 2, the HRs and 95% CIs of specific depressive symptoms with CV events are visualized in a forest plot.

When each depressive symptom was entered as a log-transformed continuous variable, the following symptoms were associated with poor cardiac prognosis: fatigue ($p = 0.0001$), appetite problems ($p < 0.0001$), sleeping difficulties ($p =$

0.03), depressed mood ($p = 0.005$), and suicidal ideation ($p = 0.02$) (Table 3). After multivariate adjustment, only fatigue and appetite problems remained significantly associated with CV events. Thus, when entered as continuous variables, 2 of 4 somatic symptoms and none of the cognitive symptoms were independently predictive of CV events (Table 3).

Discussion

In a sample of 1,019 patients with stable CHD, we evaluated the association between specific symptoms of depression and CV events. Both somatic and cognitive symptoms were associated with an increased risk for CV

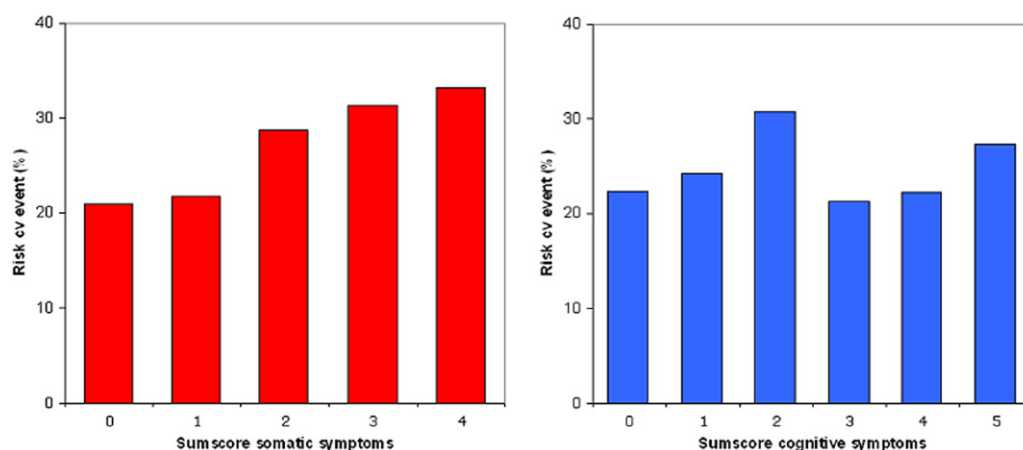


Figure 1 Age-Adjusted Annual Rate of CV Events (MI, Heart Failure, Stroke, Transient Ischemic Attack, or Death) During an Average of 6.1 Years of Follow-Up by Number of Somatic or Cognitive Depressive Symptoms

The somatic sum score is the number of somatic symptoms with scores ≥ 2 ; the cognitive sum score is the number of cognitive symptoms with scores ≥ 2 (or ≥ 1 for suicidal ideation). CV = cardiovascular; MI = myocardial infarction.

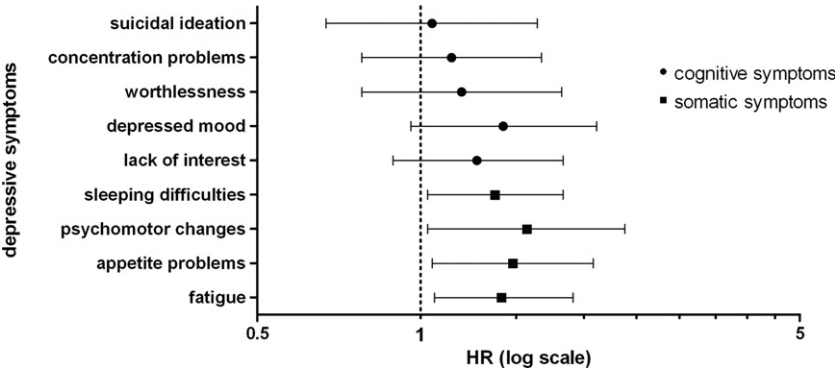


Figure 2 Association Between Specific Depressive Symptoms (Entered as Dichotomous Variables) and CV Events

Hazard ratios (HRs) with 95% confidence intervals, adjusted for age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, aspirin, beta-blocker use, statin use, and renin-angiotensin system inhibitor use. Abbreviations as in Figure 1.

events. However, after adjustment for CV risk factors and disease severity, somatic symptoms appeared to be more strongly predictive of CV events than cognitive symptoms of depression. Fatigue, appetite problems, and sleeping difficulties were the symptoms most strongly predictive of CV events. These results may be of importance for identifying depressed patients who are at highest risk for developing CV events and for identifying potential therapies to improve CV outcomes in patients with CHD.

Earlier studies have found that somatic symptoms of depression are more strongly predictive of CV events than cognitive symptoms of depression (14,16–18). However, given the high prevalence of somatic symptoms such as fatigue, loss of appetite, and sleeping difficulties in patients after MI, it was unclear whether these findings were restricted to this patient population. Our study extends these findings to outpatients with stable CHD by demonstrating that somatic symptoms are more strongly predictive of CV events in this patient population.

It is difficult to ascertain whether somatic depressive symptoms are due to depression or to worse underlying heart disease. Indeed, on the basis of our findings, one might conclude that general somatic malaise or fatigue (not depression) is the predictor of poor outcomes. However, we tried to overcome this difficulty by carefully measuring and adjusting for history of MI, diabetes, left ventricular ejection fraction, smoking, body mass index, and use of cardioprotective medications. The extent to which differences in these variables explained the effect of somatic symptoms on CV events appeared to be limited, as bivariate and adjusted effects on CV prognosis were highly comparable. In addition, we purposefully enrolled a uniform sample of patients with stable CHD so that the association between depressive symptoms and cardiac prognosis would not be confounded by the severity of a recent acute coronary event. Finally, although fatigue, appetite problems, and sleeping difficulties were the strongest predictors of CV events, these were also the most common depressive symptoms in this population.

Table 3 Bivariate and Multivariate Associations of Specific Depressive Symptoms (Entered as Continuous Variables) With CV Events

Symptom	HR* (95% CI)	p Value*	HR† (95% CI)	p Value†
Somatic symptoms				
Fatigue	1.21 (1.10–1.33)	0.0001	1.15 (1.04–1.27)	0.007
Appetite problems	1.27 (1.15–1.41)	<0.0001	1.17 (1.06–1.30)	0.003
Psychomotor agitation/retardation	1.14 (1.00–1.29)	0.05	1.12 (0.98–1.28)	0.10
Sleeping difficulties	1.11 (1.01–1.21)	0.03	1.07 (0.98–1.18)	0.14
Cognitive symptoms				
Lack of interest	1.11 (0.99–1.25)	0.07	1.04 (0.93–1.17)	0.48
Depressed mood	1.19 (1.05–1.33)	0.005	1.13 (1.00–1.28)	0.05
Worthlessness	1.11 (0.98–1.26)	0.09	1.10 (0.97–1.25)	0.15
Concentration problems	1.02 (0.90–1.15)	0.75	1.00 (0.88–1.13)	0.94
Suicidal ideation	1.25 (1.03–1.53)	0.02	1.14 (0.94–1.39)	0.19

*Adjusted for age and sex. †Adjusted for age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking aspirin, beta-blocker use, statin use, and renin-angiotensin system inhibitor use. Abbreviations as in Tables 1 and 2.

For example, depressed mood was associated with a 32% increased rate of CV events (HR: 1.32; 95% CI: 0.97 to 1.80; $p = 0.08$), but only 114 participants had depressed mood. In contrast, fatigue was associated with a 34% increased rate of CV events, but the 267 participants with fatigue yielded a tighter CI (HR: 1.34; 95% CI: 1.07 to 1.67; $p = 0.01$). Thus, the lack of an association between cognitive symptoms and CV events may be due in part to smaller number of patients with cognitive symptoms.

In this study, specific depressive symptoms on the basis of the PHQ were used. Major depressive disorder as measured by the computerized Diagnostic Interview Schedule did not predict CV events in the Heart and Soul Study (22), whereas self-reported depressive symptoms as measured by the PHQ strongly predicted CV events. It is unclear why this discrepancy occurred. It is possible that participants felt more comfortable reporting depressive symptoms on an anonymous questionnaire than in a face-to-face interview, making the interview a less accurate measure of depression.

Only 1 randomized trial has been adequately powered to evaluate the effect of depression treatment on CV prognosis in CAD patients. The Enhancing Recovery in Coronary Heart Disease Patients trial showed that cognitive behavioral therapy decreased depression and improved social support but did not affect CV prognosis. One possible explanation for the lack of benefit is that patients with CHD may have depressive symptoms below the threshold levels required for antidepressant treatment to be of benefit. Two recent studies (24,25) have suggested that patients with lower grade depression may not benefit from antidepressant treatment as much as those with more severe symptoms. If most patients with CHD have low levels of depressive symptoms, then antidepressant treatment might not be effective. Although some nonrandomized studies of post-MI patients have shown that use of antidepressants or a reduction in depressive symptoms was associated with a decreased risk for CV events (26–28), the observational design of these studies prevents a firm conclusion regarding causality.

Our present findings provide further support for the conceptualization of depression as a heterogeneous syndrome in which some aspects may be more strongly related to CV prognosis than others. This raises the possibility that to improve CV outcomes, interventions for depression should be specifically directed at somatic symptoms. Cognitive depressive symptoms, such as feelings of worthlessness and suicidal ideation, have been specific targets for intervention in psychotherapy (29), while exercise interventions, for example, may specifically improve somatic symptoms, perhaps even irrespective of depression (22,30). However, interventions for depression such as cognitive behavioral therapy or antidepressant medication therapy probably affect both cognitive and somatic symptoms, so the specificity with which somatic symptoms can be targeted with standard interventions for depression is unclear. Perhaps efforts should be made to improve rates of exercise uptake in patients with CHD, regardless of depression status, partic-

ularly given the known CHD benefits of exercise and the very low rate of adherence to this basic recommendation in both depressed and nondepressed patients.

To achieve a better understanding of the syndrome of depression and to develop effective treatments, it is important to identify potential mechanisms that may underlie the association between depression and coronary disease (31). Earlier studies examined how depression may lead to adverse clinical outcomes (32–35). In a previous report from the Heart and Soul Study, it was concluded that somatic depressive symptoms were associated with lower heart rate variability, whereas cognitive depressive symptoms were not (19). There are also studies that point to inflammation as an important mechanism underlying the relation between depression and CV prognosis (36). Inflammation also may be more strongly associated with somatic than with cognitive depressive symptoms (33). Taken together, these results suggest that individual symptoms of depression may have differential associations with several mechanisms, leading to a worse cardiac prognosis. Understanding the mechanisms that may lead to the worse cardiac prognosis observed in depressed patients with CHD will be crucial for the design of future trials (31). Future studies are therefore needed to evaluate the mechanisms that may be involved in the deleterious effects of sleeping difficulties, fatigue, appetite problems, and psychomotor changes on CV prognosis.

The strengths of this study include the cohort size, the prospective ascertainment of CV morbidity and mortality with a large number of events, and the detailed baseline assessment that allowed adjustment for important confounding variables.

Study limitations. First, this study included only outpatients with stable CHD, so we cannot comment on the differential effects of depressive symptoms in healthy people or in patients after acute coronary syndromes.

Second, the participants in this study were mainly older men. Therefore, the results may not be generalizable to women or to other patient populations. However, we adjusted for age and sex and found no indication for any interaction with age or sex.

Third, although depressive symptoms are independently associated with poor CV prognosis in patients with CHD, we cannot completely rule out the possibility that this association is confounded by worse underlying CV disease (37) or other comorbidities (38).

Finally, although the HRs and p values suggest that somatic symptoms were more strongly associated with depression than cognitive symptoms, the CIs surrounding these estimates had substantial overlap, so further research is necessary before any definitive conclusions can be drawn.

Conclusions

We found that somatic symptoms of depression were responsible for the increased risk for CV events in patients with stable CHD. Hopefully, this finding will lead to the development of

new treatments for depression in patients with CHD. The results of this study indicate the need for future research directed at the identification of the underlying pathophysiological processes by which somatic depressive symptoms contribute to prognosis in patients with CHD and to the testing of interventions to alleviate the associated risk.

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